REMARKS

Claims 1, 2, 4-7, 30, 31, 38, 39, 41-45, 47, and 112-118 are pending and under examination. No amendments are made at this time.

The Office Action has maintained the rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 and 116-118 under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240, and withdrawn the rejection over amended claims 114-115 in view of the added limitation that the human TCR alpha locus present in the transgenic animal contains all of the human TCR alpha V region, J region, and C region genes.

Applicant respectfully disagrees. None of the references in any combination can make obvious the instantly claimed invention.

McMurry is relied to support the teachings of Littman et al and to provide evident that human TCR genes can rearrange in mouse T cells using the endogenous mouse recombination machinery. The Office Action further states that McMurry et al. does not teach and was not cited for teaching any effect of the expression of functional human delta chains on T cell development in the mouse. (Page 6 of previous office action)

However, the human TCR minilocus transgene of McMurry was **intentionally made defective such that it could not generate functionally rearranged protein**. The Office Action states, "Since the authors felt the need to prevent functional rearrangement of the human delta loci, it must have been the authors expectation or prediction that productively rearranged TCR delta could affect allelic exclusion of the endogenous mouse loci which would skew their results". As indicated in the response of Jan. 22, 2009, it is known that productive rearrangement of one TCR delta allele does not inhibit rearrangement of the other TCR delta allele (see abstract of Sleckman

et al. 1998. J. Exp. Med. 188: 1465, provided previously). Thus, it is not clear how or why McMurry et al. would expect or predict a productively rearranged human TCR delta loci could affect allelic exclusion of endogenous mouse TCR delta or another TCR loci.

The Office Action further states that neither McMurry et al. nor McMurry references give any indication or evidence that human TCR expression might negatively affect T cell development. However, as described in previous responses, Lauzurica and Krangel (June 1994, J. Exp. Med. 179, 1913-1921) cited in McMurry et al. state that the reason for introducing the frameshift mutations into the human TCR minigene loci was to "**prevent a rearranged transgene from encoding a functional TCR protein and thereby influencing thymic development**" (page 1914 second column). Additionally, Roberts et al. (Jan. 1997, J. Exp. Med. 185, 131-140, copy enclosed) cited in McMurry et al. (ref. 41) state that mutations were introduced to "prevent a rearranged transgene from encoding a functional TCR protein that could alter normal T cell development in transgenic mice" (page 133 second column). Although the Office Action has focused on the strategy of using the mutant TCR minilocus to avoid allelic exclusion of the endogenous TCR gene described in Lauzurica and Krangel (Jan. 1994, J. Exp. Med. 179, 43-55, provided previously), these other citations clearly indicate that the defective loci was used to **prevent the functional TCR protein from influencing thymic development and altering normal T cell development**. The authors give no indication that this strategy was employed merely to avoid skewing their results.

While the Office Action is not relying on McMurry et al. for teaching expression of functional human TCR chains in the mouse, it is clear from these references that McMurry et al. believed that productively rearranged transgenic human TCR loci could generated functional TCR protein capable of altering normal T cell and thymic development. Thus, based on these teachings, a skilled artisan would expect that a transgenic human TCR locus capable of productive rearrangement and expression of a functional TCR protein could affect TCR gene allelic exclusion as well as normal T cell and thymic development.

Additionally, the Office Action states that the prior art teaches that transgenic mice comprising a rearranged human TCR beta transgene produced mature T cells expressing TCR comprising the recombinant human TCR chain which had successfully passed through positive and negative selection and were capable of mounting proliferative response to antigen (Rothe et al. 1993. Int Immunol. 5, 11-17, Viney et al. 1992. Hybridoma 11, 707-713, provided previously). However Viney et al. only described using cells from a rearranged human TCR β chain transgenic mouse to produce anti-TCR antibodies. There was no teaching regarding the ability of the transgenic TCR to respond to antigen. Rothe et al. describe generation of a transgenic mouse carrying a rearranged human TCR β chain gene. T cells from this mouse expressed the human TCR β chain and responded to allogeneic targets in a mixed lymphocyte reaction, however, no data were presented indicating that these T cells could react to peptide presented in the context of MHC molecules. Additionally, Rothe et al. stated that the expression of the human TCR β chain in transgenic mice had a strong impact on the number and phenotype of T cell in the thymus (page 15 first column). **These results suggest that the human TCR transgene negatively impacts T cell development in the thymus**. Neither Rothe et al. nor Viney et al. provide any teaching regarding expression of rearranged or unrearranged human TCR α genes or unrearranged human TCR β genes in transgenic animals. Moreover, it is well established in the literature that rearranged murine TCR genes when expressed as transgenes lead to differences in early T cell development (i.e. accumulation of TCR-positive CD4-CD8- (double negative) cells), T cell selection and responses and the T cell repertoire (see for example, Lacorazza et al. 2001. J. Immunol. 166: 3184–3193, copy enclosed). Some of these effects are due to the artificial early expression of the rearranged TCR genes in thymocytes during T cell development. Thus, the prior art related to expression and function of rearranged TCR transgenes is not relevant to the ability of unrearranged human TCR α and β loci to undergo productive rearrangement and functional TCR production in transgenic mice necessary for T cell development, T cell maturation or antigen stimulated responses.

Withdrawal of the rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 and 116-118 for obviousness is respectfully requested.

Claims 114-115 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240 as applied to claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118 above, and further in view of the NCBI database Accession Number NG 001332.

The NG-001332 sequence cited by the examiner in rejection of claims 114-115 was first available Jun 10, 2002, after the filing date of the application (see attached). Withdrawal of the rejection is respectfully requested.

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 04-1105 the fee for a three month extension of time for response, small entity, referencing Docket No. 49663(48340).

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,
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